ORIGINAL ARTICLE

Rheumatology Quarterly

DOI: 10.4274/qrheumatol.galenos.2024.92485
Rheumatology Quarterly 2024;2(3):130-6

# THE EFFECTS OF MICROALBUMINURIA AND INFLAMMATORY MARKERS ON CAROTIS INTIMA MEDIA THICKNESS IN FAMILIAL MEDITERRANEAN FEVER

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## Abstract

**Aim:** This study aimed to investigate the presence of early atherosclerosis due to inflammation and its relationship with microalbuminuria in newly diagnosed Familial Mediterranean fever (FMF) patients.

**Material and Methods:** Seventy-seven FMF patients who were newly diagnosed and 34 healthy volunteers were enrolled in this study. In all study groups, microalbuminuria in 24 hours urine sample, C-reactive protein (CRP), hemogram, erythrocyte sedimentation rate (ESR), fibrinogen, routine biochemistry, and lipid panels were performed. Carotid intima media thickness (IMT) was measured in both groups using the same ultrasonography device using a 12 MHz linear probe. To minimize technical errors, patients were also evaluated by the same radiologist. In all patients, both the main carotid arteries and internal carotid arteries were examined for morphology.

**Results:** IMT, triglyceride, high-density lipoprotein, low-density lipoprotein, and cholesterol levels did not differ significantly between the groups ($p>0.05$). The fibrinogen levels of the FMF group were significantly higher ($p<0.01$). The CRP levels of the FMF group were significantly higher ($p<0.05$). On the other hand, ESR, red blood cell, hematocrit, hemoglobin, platelet, and microalbumin measurements did not show statistically significant difference according to the groups ($p>0.05$). The positive 15.2% correlation between IMT and fibrinogen levels was not statistically significant ($r=0.152$; $p=0.109$; $p>0.05$). There was no statistically significant relationship between IMT and CRP and ESR levels. The negative 10.2% difference between IMT and microalbumin values was not statistically significant ($r=-0.102$; $p=0.289$; $p>0.05$).

**Conclusion:** The significant difference between the inflammatory markers, such as fibrinogen and CRP between FMF patients and the healthy controls demonstrates that subclinical inflammation continued in the patient group, even if the patient did not develop FMF attack. Although microalbuminuria is known to be an early diagnostic criterion of atherosclerosis, no correlation was detected between microalbuminuria and inflammatory markers and carotid IMT. In summary, since no remarkable correlation was found between FMF-related inflammation and carotid IMT, we do not recommend clinical follow-up with carotid Doppler ultrasound in addition to routine outpatient controls.

**Keywords:** Familial Mediterranean fever, microalbuminuria, carotid intima media thickness, subclinical inflammation

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**Received:** 11.08.2024 **Accepted:** 23.10.2024

## INTRODUCTION

Familial Mediterranean fever (FMF) is an autosomal recessive disease that affects especially the Sephardic Jews, Arabs, Turks, and Armenians settled around the Eastern Mediterranean (1). Recurrent fever, peritonitis, pleuritis, arthritis, pericarditis and skin findings are observed. Attacks usually occur in late childhood and adolescence. In 60-70% of the cases, symptoms were observed in the first 10 years, in 80-90% of the cases before the age of 20 years. The mean age at onset was 4.5 years (2).

Several factors have been implicated in the etiopathogenesis of FMF. In FMF, mutations in the Mediterranean fever gene disrupt the structure of the pyrin /marnostrin molecule, resulting in increased leukocyte migration to serosas and a prolonged and inappropriate response to inflammatory stimulation. Thus, acute phase reactants, such as C-reactive protein (CRP), serum amyloid A (SAA), and the erythrocyte sedimentation rate (ESR), are increased in patients with FMF. In this context, studies on the cytokines responsible for acute phase responses were performed, and mediators such as interleukins-1,8 and tumor necrosis factor-alpha were found to be high during the attack periods. In other words, FMF is a chronic inflammation-associated disease, and amyloidosis development is indispensable in patients who do not receive effective treatment regularly. Early diagnosis of the disease and its complications is important because the disease emerges at a very young age and has a chronic course. Recently, the relationship between atherosclerosis and inflammation has become a widely accepted clinical condition (3). However, there are contradictory results in the effect of inflammation on the development of atherosclerosis in FMF characterized by chronic inflammation (4-6). There are also reports that microalbuminuria may be a sign of early diagnosis for atherosclerosis (7,8).

Microalbuminuria due to renal involvement in FMF is the most common finding of organ damage. There are no strong and large population-based clinical studies on the role of albuminuria in FMF in the terms of the early diagnosis of concomitant atherosclerosis.

Due to the fact that it is easy to use, safe and inexpensive in the early diagnosis of atherosclerosis, the measurement of the wall thickness of the carotid artery with Doppler ultrasonography (USG) is a frequently used imaging method (9). Therefore, in this study, we evaluated the relationship between carotid artery wall thickness and microalbuminuria for the presence of atherosclerosis in newly diagnosed FMF who are free of symptoms.

## MATERIAL AND METHODS

This study included 34 healthy volunteers and 77 patients with FMF who were newly diagnosed according to the Tel Hashomer criteria at internal disease outpatient clinics between 2010 and 2012 and were not yet treated with colchicine. Anamnesis was performed in all cases, and full physical examinations, necessary laboratory tests, and imaging studies were performed. Patients with a history of diabetes mellitus, hypertension, peripheral artery disease, systemic vasculitis, chronic renal failure, nephrotic syndrome, acute or chronic other inflammatory diseases, psychiatric disorders, malignancy, pregnancy, smoking, anti-inflammatory drug use, morbid obesity, and those aged <16 or >65 years were not included in the study.

In all study groups, we assessed microalbuminuria in 24 hours urine samples, CRP, hemogram, ESR, fibrinogen, blood glucose, low-density lipoprotein cholesterol (LDL-C), triglyceride, high-density lipoprotein cholesterol (HDL-C), tests were performed. CRP levels were measured via the nephelometric method (Colter Immage 800, Beckman, USA) in a thin dry tube after centrifugation in serum. ESR levels per hour were analyzed using the Westergren method (Vacuplus ES-120, Turkey). Complete blood count was performed using an automated analyzer (Siemens Advia 2120, Germany) in the hemogram tube for 24 parameters. Fibrinogen levels were determined using the Clauss method (Amax 200, Germany).

Triglyceride levels by glycerol phosphate oxidase method, HDL-C levels by accelerator selective detergent method, LDL-C levels by enzymatic method, and microalbuminuria by immunoturbidimetric method were measured using an auto analyzer (Abbott architect C8000 biochemistry USA).

Carotid intima media thickness (IMT) was measured in both groups. This measurement was performed on the same USG device (Aplio XG, Toshiba, Japan) using a 12-MHz linear probe. For the measurements, patients were visualized in the supine position with their head facing the opposite side of the examined side and the right and left carotid arteries. In all cases, both common carotid arteries (CCA) and internal carotid arteries were examined for morphology. Measurements were made on B-mode images obtained from the posterior wall in the first 1 cm segment of the internal carotid artery and in the proximal region of approximately 1 cm proximal to the carotid bifurcation. The defined measurements were repeated for both carotid arteries. The IMT value was then evaluated by taking into consideration the average of all the measurements. The presence of plaque or stenosis in the carotid system during the examination was also noted. To minimize technical errors, all measurements were performed by a single radiologist. The upper limit of normal for carotid artery IMT was 0.8 mm. Demographic characteristics, metabolic and inflammatory markers, and IMT measurements of both groups were compared. In addition, the correlation between microalbuminuria and inflammatory markers and carotid IMT

was investigated in patients with FMF. Written informed consent forms were obtained from all participants before the study. This study was approved by the Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 16914, date: 18.10.2012).

### Statistical Analysis

The Number Cruncher Statistical System 2007 & Power Analysis and Sample Size 2008 statistical software (Utah, USA) was used for statistical analysis. Student's t-test was used to compare descriptive statistical methods (mean, standard deviation, median, frequency, ratio), as well as normal distribution of parameters with normal distribution. The Mann-Whitney U test was used to compare parameters that did not show normal distribution. For qualitative data comparison, Fisher's Exact, chi-square test was used. Statistical significance was defined as $p<0.05$ for all analyses.

## RESULTS

Seventy-seven patients with FMF and 34 healthy controls were included in the study. A comparison of the demographic characteristics of the groups is presented in Table 1. A statistically significant intergroup difference was observed ($p<0.01$). The patients in the FMF group were significantly older.

There was a statistically significant difference in the levels of fibrinogen (Figure 1) and CRP (Figure 2) in the FMF group compared with the control group ($p<0.01$ and $p<0.05$, respectively). However, no significant difference was observed between the carotid IMT groups (Table 2).

There was no statistically significant relationship between carotid IMT and fibrinogen levels, although a positive value of 15.2% was detected. In addition, the correlations of carotid IMT with CRP and ESR were not statistically significant. Furthermore, carotid IMT and microalbumin levels were negatively correlated, with a value of 10.2% being not statistically significant. In summary, neither inflammatory markers nor microalbuminuria was correlated with IMT in patients with FMF (Table 3).

## DISCUSSION

In this study, when patients with FMF and healthy controls were compared in terms of carotid IMT (surrogate marker of early atherosclerosis), although some inflammatory markers were significantly higher in the FMF group, no significant difference was found between the two groups. There was no correlation between inflammatory markers and carotid IMT. There are very few studies in the literature on this issue. While the present study was consistent with the results of several clinical studies, it was incompatible with the results of other studies.

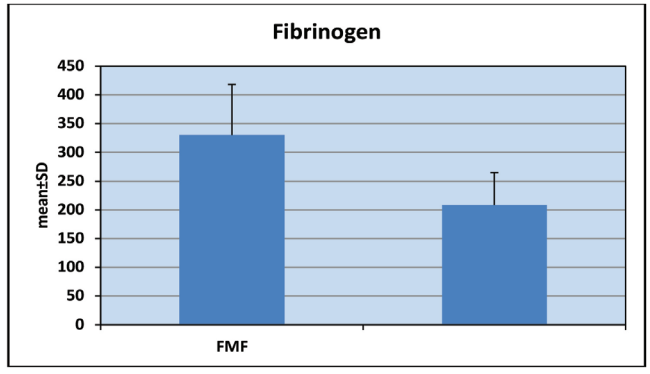


**Figure 1.** Distribution of fibrinogen levels in the two groups
FMF: Familial Mediterranean fever

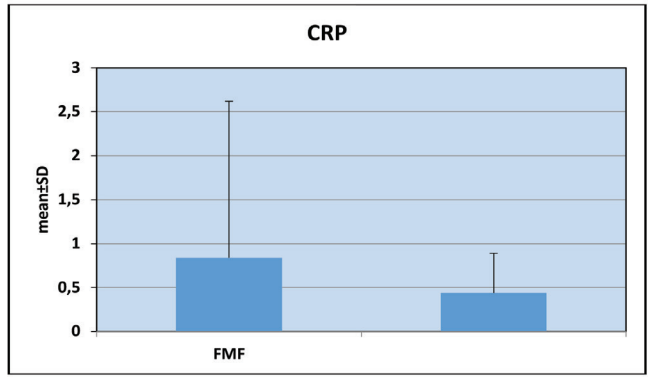


**Figure 2.** Distribution of CRP levels in both groups
CRP: C-reactive protein

**Table 1. Distribution of demographic variables in the two groups**

| | | FMF (n=77) | HC (n=34) | p-value |
|---|---|---|---|---|
| **Age (years)** | | 31.71±9.32 | 41.79±9.93 | 0.001** |
| **BMI (kg/m²)** | | 26.14±4.99 | 28.19±3.55 | 0.032* |
| **[a]Gender** | Males, n (%) | 34 (44.2) | 10 (29.6) | 0.143 |
| | Female, n (%) | 43 (55.8) | 24 (70.6) | |

Student t-test, [a]Yates test, *p<0.01, **p<0.01. Data presented as mean ± SD and number (percentage),
FMF: Familial Mediterranean fever, HC: Healthy controls, BMI: Body mass index, SD: Standard deviation

**Table 2. Distribution of metabolic and inflammatory markers and carotid artery IMT**

| | | FMF (n=77) | HC (n=34) | p-value |
|---|---|---|---|---|
| IMT | | 0.55±0.66 | 0.54±0.08 | 0.526 |
| [a]TG; (Median) | | 121.93±78.88 (102.00) | 134.88±64.62 (115.50) | 0.099 |
| HDL-C | | 43.01±12.85 | 47.09±9.80 | 0.102 |
| LDL-C | | 102.86±33.26 | 111.44±32.79 | 0.211 |
| TC | | 170.26±43.25 | 185.51±36.56 | 0.076 |
| Fibrinogen | | 330.32±88.02 | 208.23±56.48 | 0.001** |
| [a]CRP; (Median) | | 0.84±1.78 (0.39) | 0.44±0.45 (0.31) | 0.038* |
| [a]ESR; (Median) | | 12.77±11.22 (8.00) | 10.82±6.60 (10.00) | 0.822 |
| WBC | | 7.41±1.99 | 7.85±1.89 | 0.282 |
| HCT | | 40.11±4.31 | 38.57±4.16 | 0.082 |
| Hgb | | 13.37±2.04 | 12.48±1.32 | 0.021 |
| [a]Plt; (Median) | | 274.96±74.22 (269.00) | 315.11±312.53 (262.00) | 0.611 |
| [a]Microalbumin; (Median) | | 14.84±16.70 (8.10) | 11.64±7.00 (11.50) | 0.920 |
| [b]Plaque | Absent, n (%) | 66 (85.7%) | 34 (100.0%) | 0.017* |
| | Present, n (%) | 11 (14.3%) | 0 (0.0%) | |

Student t-test, [a]Mann-Whitney U test, [b]Fisher's Exact test, *p<0.01, **p<0.01. Data presented as mean ± SD and number (percentage), IMT: Intima media thickness, FMF: Familial Mediterranean fever, HC: Healthy controls, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TC: Total cholesterol, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, HCT: Hematocrit, Hgb: Hemoglobin, Plt: Platelet, TG: Triglyceride

**Table 3. Evaluation of the correlation between inflammatory markers and microalbuminuria and carotid IMT in patients with FMF**

| FMF patients (n=77) | IMT | |
|---|---|---|
| | r | p-value |
| Fibrinogen | 0.152 | 0.109 |
| [a]CRP | 0.036 | 0.705 |
| [a]ESR | 0.054 | 0.574 |
| [a]Microalbumin | -0.102 | 0.289 |

r=Pearson correlation, [a]r=Spearman's rho. IMT: Intima media thickness, FMF: Familial Mediterranean fever

Bilginer et al. (4) reported that all acute-phase reactants (ESR, CRP, fibrinogen and SAA) were significantly higher in patients with FMF than in healthy controls, although there was no FMF attack. They found a positive correlation between internal carotid artery IMT and ESR and fibrinogen levels. These findings were consistent with ongoing subclinical inflammation, although no apparent FMF attack was noted. They thought that this subclinical inflammation could explain the increase in carotid IMT detected in patients with FMF. They concluded that suppression of inflammation with adequate doses of colchicine could prevent this complication and recommended measuring carotid IMT to detect early arterial changes in patients with FMF (4).

In a study by Langevitz et al. (10) on patients with FMF receiving colchicine despite treatment, they thought that they would find increased ischemic heart disease due to continuous inflammation. However, as a result of the study, there was no increased incidence of ischemic heart disease in FMF patients. On the contrary, the authors found that the prevalence of ischemic heart disease in patients with FMF decreased by 15.5% compared with the control group. They thought that this was due to the effect of colchicine treatment, which began at a young age and continued for life. These patients were exposed to both inflammatory protective effects and side effects, such as nausea, anorexia, and diarrhea (10). Although, in the study of Langevitz et al. (10) found that ischemic heart disease was lower than expected in adult patients with FMF, we believe that these patients should be followed up objectively.

In a case report by Ordu et al. (11), a patient with acute coronary syndrome (ACS) diagnosed with FMF after 20 years of age partially responded to colchicine treatment. Therefore, they thought that the cause of early ACS in patients may be due to chronic inflammation (11). As in this case, there are clinical studies showing that administration of aspirin to patients with late diagnosis or unresponsive to colchicine treatment and with

high CRP levels significantly reduces CRP levels, and in parallel, the risk of ischemic events decreases in these patients (12,13).

Therefore, patients with a diagnosis of FMF have a high risk of early ischemic heart disease; suggested that these patients could be followed more frequently by measuring carotid IMT and CRP levels, which are indicators of early atherosclerosis. ACS should be considered in the differential diagnosis of patients with FMF presenting with angina, and patients should be carefully evaluated in this respect.

In a study performed by Akdogan et al. (6) in the same hospital adult population, they found an increased carotid IMT in patients with FMF compared with healthy volunteers, independent of known risk factors for atherosclerosis. At the same time, as expected, acute-phase reactants were found to be high in patients with FMF. It was reported that this change in the IMT of the carotid artery in patients with FMF was due to ongoing inflammation at a low level. In addition, the similarity of serum lipid changes in patients with FMF and other chronic inflammatory diseases, such as rheumatoid arthritis (14). Although they thought that the ongoing inflammation in patients with FMF could cause an increase in carotid IMT due to low HDL-C levels, apart from the disease itself, they did not detect such a situation in the aforementioned study (6). Although low HDL-C levels were observed in our study, no statistically significant difference was found.

As stated earlier, in the study of Peru et al. (5), it was emphasized that environmental factors may play an important role in the emergence of FMF, and FMF patients with the same genetic background may differ according to the region in which they live or their living habits. In this context, a study reported that Armenian-born FMF patients in the USA develop less amyloidosis than FMF patients in Armenia (15). Therefore, the inconsistencies in the results of the studies can be explained by the differences in the lifestyles and socioeconomic status of the patients in the study groups. In this study (5), the carotid artery IMT values of pediatric FMF patients were significantly increased compared with the age- and sex-appropriate healthy control group, which supports the study of Akdogan et al. (6).

In another study conducted by Ugurlu et al. (16), patients with FMF and SLE were investigated. Carotid and femoral artery ITM was increased in both groups. Plaque increase was also detected in patients with SLE, but no increase was observed in patients with FMF. The results of this study are similar to those of other studies (16).

In a study designed by Oren et al. (17), patients with FMF receiving colchicine treatment and individuals in the healthy control group were compared by collecting urine during the day and night when they were active, and no significant difference was found. However, a slight increase was detected in urine collected in the morning compared with the night in the control group. This increase was found to be significantly different in patients with FMF than at night, and this exaggerated response was expressed as a sign of mild glomerular damage in patients with FMF (17). Similarly, Saatci et al. (18) reported an increase in microalbuminuria in exacerbation after colchicine treatment was discontinued in patients diagnosed with FMF.

Microalbuminuria is associated with renal damage and endothelial dysfunction in FMF patients. In another study conducted for this purpose, Güneş et al. (19) measured flow-mediated dilatation (FMD) showing endothelial dysfunction from the left arm brachial artery using Doppler ultrasound and compared it with microalbuminuria and found that this value was lower in FMF patients with microalbuminuria than in patients without microalbuminuria. Therefore, the authors predicted that FMD could be used for the early detection of renal damage and endothelial dysfunction (19).

Furthermore, in a study evaluating early markers of atherosclerosis such as FMD, nitroglycerin-induced endothelium-independent peripheral vasodilation, and CCA IMT in patients with FMF, no abnormalities were found in these parameters when receiving regular daily colchicine therapy (20). In this study, the authors stated that it may be possible that pyrin or any other protein that plays a role in the pathogenesis of FMF may interact with components in the pathogenesis of atherosclerosis and prevent its development. They believed that FMF attacks are unresponsive to other drugs, but their dramatic response to colchicine, which protects against FMF attacks and prevents the development of amyloidosis, may support the idea that the inflammatory process in FMF has a different mechanism from other rheumatological diseases. They argued that inflammation in patients with FMF could be explained by another possible mechanism. Severe inflammation in an FMF attack usually subsides in 3-4 days, but subclinical inflammation continues even when patients use regular colchicine.

However, low inflammation levels may not be sufficient to accelerate the development of atherosclerosis.

In addition, studies have shown that a decrease in urinary glycosaminoglycan (GAG) levels and the development of microalbuminuria may be the findings pointing to the development of amyloidosis in patients with FMF, and that GAG levels will increase and microalbuminuria will regress with increasing colchicine doses (21,22).

Apart from these, it is useful to mention some limitations of our clinical study. First of all, in this study, although high inflammatory

markers suggest that there is continuous inflammation, there were visible differences in microalbuminuria and carotid IMT between the FMF group and the control group, but these differences were not significant because the study group was not sufficiently large or the disease was newly diagnosed, and the effects of the inflammatory process were observed. This may be due to the fact that not enough time has passed. Similar to some other studies (4-6,18) in a study to be conducted in a larger group, increased carotid IMT may be detected in the FMF group. However, given that this group also started using colchicine, Sari et al. (20), it is possible that no difference was detected due to the protective effect of colchicine.

Second, although plaque was detected in the carotid artery in 11 patients in the FMF group, there was no plaque in the control group, and widespread irregularity was present in 1 patient in whom we detected amyloidosis in this present study, although there was no visible plaque on imaging. The insignificance of this difference may be due to the insufficient number of participants in our study groups.

Third, carotid IMT may have affected the results because the control group was older than the FMF group. The fact that FMF disease is also affected by environmental factors other than genetic factors may be reflected in the results because our patient population consisted of people living in a relatively low socioeconomic environment.

Lastly, we could not investigate the FMF gene mutation in patients in the control group because of the high cost; however, it is possible that there are carriers in this group, and in this case, the results may be affected because such individuals will also have subclinical inflammation.

As mentioned previously, the relationship between microalbuminuria and atherosclerosis has been demonstrated in various studies in the literature. Although this relationship has not yet been proven in patients with FMF, it is highly probable that the vascular problems observed in this group of patients are observed simultaneously with microalbuminuria in patients with this disease and renal involvement. If this relationship is proven, a detailed cardiac evaluation, questioning of other risk factors, and, if necessary, invasive procedures will be performed without loss of time in the microalbuminuria group. In the opposite case; In the FMF patient with a vascular problem, necessary precautions will be taken by looking for microalbuminuria if it has not been done. In order to be clinically guiding, such a relationship must be proven. This requires a larger study group and longer exposure to the effects of FMF disease.

As is well known, patients with renal amyloidosis are at the highest risk of vascular damage. As a result, due to the nature of FMF, patients with this disease should be considered at increased risk of early vascular changes and atherosclerosis. From this perspective, patients should be evaluated for other inflammatory diseases throughout their lives. For this purpose, our study was important in terms of carotid artery IMT measurement, which is recommended as a non-invasive and early diagnostic method and is predictive of subclinical inflammation, especially in cases of microalbuminuria (23).

## CONCLUSION

In summary, we investigated whether there is an increase in carotid IMT due to ongoing inflammation in patients with FMF and whether this condition is associated with microalbuminuria. The significant difference in inflammatory markers, such as fibrinogen and CRP, between our patient population and the control group indicates that subclinical inflammation continues in the patient population, even when the patient is not in an attack. In conclusion, given that no significant correlation was found between inflammation and carotid IMT, we do not recommend regularly ordering carotid Doppler USG in addition to routine outpatient clinic checks due to the cost of providing healthcare services.

### Footnote

**Ethics Committee Approval:** This study was approved by the Ümraniye Training and Research Hospital Clinical Research Ethics Committee (approval number: 16914, date: 18.10.2012).

**Informed Consent:** Informed consent forms were obtained from the patients.

### Authorship Contributions

Surgical and Medical Practices: T.M.C., Concept: S.B., Design: S.B., Data Collection or Processing: T.M.C., Analysis or Interpretation: T.M.C., Literature Search: T.M.C., B.G., Writing: T.M.C.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study received no financial support.

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